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# BNA Bulletin

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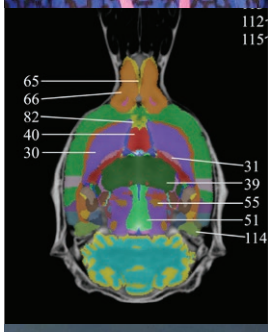


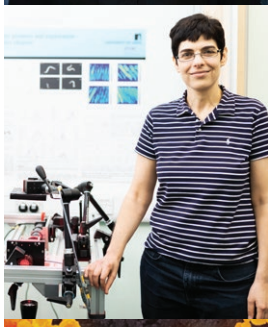

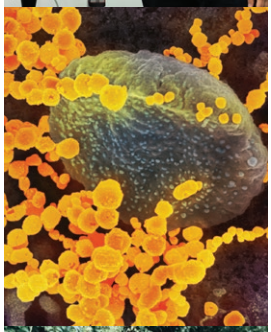


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Seals are expert divers, and capable of remarkable control over their autonomic nervous systems. See page 26. Image: Joseph Skinner/ WikiMedia Commons.


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# MAPping the course of dementia

Multi-omics technologies could provide new insights into the causes and progression of Alzheimer's disease.

Alzheimer's disease remains stubbornly resistant to the development of effective therapeutics, with drug development failure rates depressingly high. In large part, this reflects an incomplete understanding of the molecular mechanisms of disease, and the links between the pathology observed and cognitive symptoms. At Imperial, **Jo Jackson** is leading a UK Dementia Research Institute (UK DRI) initiative that is using a variety of 'omics' technologies to characterise the molecular changes occurring through disease progression, alongside her own research on degeneration of the synapse.

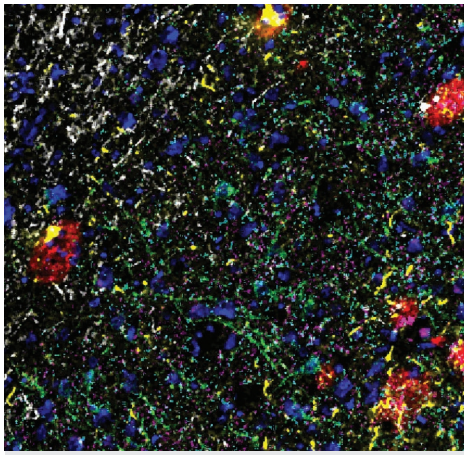
After a PhD at Imperial and postdocs at Lund in Sweden and back at Imperial, Dr Jackson had the opportunity to set up a two-photon imaging facility at Eli Lilly. She soon became a permanent employee, running a research programme focused primarily on the role of synapse loss in Alzheimer's disease.

In 2019, she decided to move back to academia, taking up her current position at Imperial, which combines leadership of the UK DRI's Multi-omics Atlas Project (MAP) and research on the synapse.

## MAPping AD

MAP is a £2m UK DRI Director's initiative. "The idea is to comprehensively characterise the pathology of human Alzheimer's post-mortem brain tissue," says Dr Jackson. Of course, plenty of work has been carried out on Alzheimer's disease pathology, but the MAP initiative differs from past efforts in several significant ways.

The first novel aspect is the range of molecular technologies that are being applied to characterise tissue samples. These include epigenetic, transcriptomic, proteomic and lipidomic analyses, providing a wealth of insights into epigenetic tags on DNA, messenger RNAs and gene expression, proteins, and lipids.



Imaging mass cytometry allows the visualisation of multiple markers on one tissue section. Here, a panel of seven antibodies has been used to visualise pathology, cytoarchitecture, axons, dendrites and synapses. Image courtesy Sulin Liu.

"Each piece of data is traceable back to the donor brain," points out Dr Jackson, "but more importantly to the specific region of that brain." The project is focusing on eight different regions of the brain affected at different stages of Alzheimer's disease, breadth of coverage that again marks MAP out from previous projects.

The goal is to trace the molecular progression of Alzheimer's disease, says Dr Jackson. "We're interested in the early stages so we can determine the molecular tipping points of the disease and the pathology. That is difficult – people usually die at the latest stages." However, looking at brain regions affected at different stages should provide some insights into disease progression. "Because we have the eight different brain regions, it means we can create a pseudo-temporal profile of the disease – we know different brain regions are affected at different stages of disease."

In addition, some donated brains are at a mid-stage of disease progression, while some control brains, which are undergoing similar intensive analysis, also show early signs of Alzheimer's pathology.

The initiative is a massive data-management challenge, with analyses being run on ten samples from eight regions in 12 Alzheimer's disease and six control brains. "When you start multiplying those numbers up, that's quite a lot of brain tissue," points out Dr Jackson.

Furthermore, each omics approach actually involves multiple technologies. The transcriptomics analysis, for example, includes both single nuclear transcriptomics and bulk transcriptomics, but there is also growing interest in 'spatial transcriptomics' – analysis of mRNAs within specific compartments of the cell.

Dr Jackson co-chaired a seminar at BNA*2021*: Festival of Neuroscience on single-cell approaches. "One of the things that came out of that session was the opportunity to look at spatial omics, in particular transcriptomics. The field is moving really fast in this space."

Studies have shown that mRNA transcripts in dendrites, axons and cell bodies can be very different, and spatial resolution is continually improving. The Imperial team is collaborating with US researchers at the Broad Institute, who have developed a high-resolution approach known as 'slide-seq'. "It's an emerging field, but it's very important to look at the localisation of these transcripts and their spatial relationship with the pathological hallmarks of the disease."

A key responsibility of Dr Jackson and her team is to create a pipeline and platform that can assimilate huge quantities of data, make sense of it, and make sure it is available for others to work with. "We're very keen on this being an open-science platform to benefit the field as a whole."

The team has been gearing up for large-scale analysis of MAP samples by

Johanna Jackson, who runs the UK DRI's Multi-omics Atlas Project (MAP).

characterising existing tissue collections. Most advanced is a multi-omic analysis of tissue samples from carriers of *TREM2* mutations, one of the most significant risk factors for Alzheimer's disease. *TREM2* codes for a receptor found on myeloid cells, highlighting the potentially key role of immune responses in the condition.

## Focus on the synapse

Alongside work on the MAP initiative, Dr Jackson is also studying synaptic changes in Alzheimer's disease, taking her past research in new directions. "Up until I joined the UK DRI, I'd done all my previous work in pre-clinical models, in transgenic mouse lines. I'm now essentially moving that into human tissue."

Her interests include how synapses are affected as pathology progresses, including differences between pre- and post-synaptic components and excitatory versus inhibitory synapses.

Recent years have seen great efforts made in understanding and targeting underlying disease mechanisms, such as the build up of beta-amyloid plaques and spread of tau pathology. Dr Jackson suggests that focusing on synapses is a valuable complementary strategy: "Everyone associates Alzheimer's disease with cognitive impairment, and what leads to cognitive impairment is the loss of synapses."

Synapse loss might be directly attributed to Alzheimer's disease pathology or a consequence of other mechanisms such as inflammation. Either way, interfering with underlying pathology may not be sufficient to address all symptoms: "Even if you can stop the disease in its tracks, patients will still have some cognitive impairment because some synapses will have been lost." She envisages that some form of combination therapy might ultimately be possible: "Ideally, if you give a disease-modifying therapy with a therapy that targets synapses, you might be able to not only stop disease progression but also restore or at least halt the changes in cognitive impairment."

As well as work with post-mortem samples, she also hopes to expand into other models of human disease, including induced pluripotent stem cells and organoids. She is also collaborating with researchers at McGill University in Canada to characterise live resected tissue obtained during brain surgery. Initially, the aim will be to check the difference in tissue quality between post-mortem and live tissue to understand the effects of sample preservation techniques on the data generated.

She is also building on her experience of imaging. She is introducing the CLARITY platform, which renders brain tissue transparent, as well as imaging mass cytometry. "The main advantage of this is that you can use up to 37 markers on the same tissue section," she explains – a big improvement on current techniques, which can visualise only a few markers at a time.

**"THE EXPERTISE THAT IS AVAILABLE ACROSS THE UK DRI IS VAST AND EVERYONE IS OPEN TO SHARING AND COLLABORATING. BASED ON HOW COMPLICATED ALZHEIMER'S IS, THAT'S THE APPROACH WE NEED TO TAKE."**

## A virtual institute

UK DRI is an innovative venture, spanning some 600 researchers at sites across the UK. "The expertise that is available across the UK DRI is vast," says Dr Jackson, "and everyone is open to sharing and collaborating. Based on how complicated Alzheimer's is, that's the approach we need to take."

A wide range of cross-centre initiatives have been established. For example, researchers in particular themes, such as the synapse and bioinformatics, interact regularly and share their differing perspectives. "It works well and you get to know people from other centres really well because you work closely with them."

Collaborations have also been established with industry, for example through joint postdocs. "There's a few of those now," says Dr Jackson. "I think industry are very much open to this model, and to getting these collaborations going."

Her own time in industry, she suggests, has been extremely valuable in her new role. "One of the things you learn to do in industry is manage these larger-scale projects. That set me up quite well for leading this project at the UK DRI."

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